

**The Response**

**1. Drawings**

Applicants are deferring the submission of Formal Drawings until the Examiner allows the application.

**2. Sequence Rules**

Applicants have submitted paper and computer readable format of sequence listing on August 8, 2000.

**3. Objection to the Specification**

The specification is objected to because of informalities. The objection is overcome in parts in view of the amendments and in parts traversed. Applicants have amended the specification to insert the priority claim in the first paragraph of the specification and the generic name of TWEEN 20®.

Applicants do not agree with the Examiner that the incorporation of references at pages 3 and 4 of the substitute specification is improper for the following reasons. A copy of pages 191-210 of "Human Chromosomes" which is cited in the application is submitted herewith. The reference discloses that Comparative Genomic Hybridization (CGH) is a conventional method known since 1990 by which a comprehensive analysis of imbalanced chromosomal material of entire genomes is permitted (Boyle *et al.*, 1990; Kievits *et al.*, 1990). The comparative genomic hybridization (CGH) methods were well known to those skilled in the art at the time the present application was filed. Therefore, the incorporation of references for the CGH method is proper and the Examiner's objection should be withdrawn.

**4. Rejections under 35 U.S.C. § 112, First Paragraph.**

Claims 1-8 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner states that pages 2-3 of the specification disclose that the identification of any change in copy number of a target sequence is achieved via performing comparative genomic hybridization; the specification does not enable this form of detection as essential subject matter has been improperly incorporated by reference. The Examiner's rejection is respectfully traversed.

As discussed above, the comparative genomic hybridization (CGH) methods were well known to those skilled in the art at the time the present application was filed. A specification need not disclose what is well known in the art. (*Hybritech, Inc., v. Monoclonal*

*Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986) An omission of minor details does not cause a specification to fail to meet the enablement requirement.

The CGH method is disclosed in *Human Chromosomes*. In the CGH method, a genomic DNA to be analyzed (test DNA) is labeled and cohybridized with differentially labeled normal DNA (control DNA) under suppression hybridization conditions to metaphase chromosome spreads from normal cells.

In the Example of the present application, a normal genomic DNA is tag-labeled by DOP PCR (step 1) and modified by digoxigenin-11-dUTP (step 2); the product obtained is control DNA. The control DNA is *in situ* hybridized on interphase nuclei of line Colo 320 (step 3). Then the hybridized nuclei are isolated and subjected to DOP PCR (step 4); the product obtained is test DNA. The test DNA is cohybridized with the control DNA under suppression hybridization conditions to metaphase chromosome spreads from normal cells (step 4: CGH analysis). Applicants have provided a working example, which includes working conditions for the claimed invention. The CGH method is a well-known method at the time of filing this application; thus it is not necessary to describe the details of the CGH method because Applicants have incorporated the references that describe the CGH method into the application.

In the working example of the application, Applicants describe the reagents, buffers and solutions for preparing a tag-labeled sequence. Applicants also describe the denaturation conditions of the genomic DNA of the Colo320 interphase nuclei, the hybridization conditions for the *in situ* hybridization, and the washing and detection conditions of the hybridized cell nuclei. Further, Applicants describe the conditions for isolating the hybridized nuclei. The CGH analysis is described in the cited references that are incorporated by references. Following the example taught in this application, an ordinary skilled person would be able to practice the invention. Although the Examiner asserts that the claimed invention is sensitive to the conditions employed in a hybridization reactions, the optimization of hybridization reactions is routine to a skilled artisan and does not constitute an undue experimentation.

Therefore, the §112, first paragraph rejection of Claims 1-8 should be withdrawn.

**5. Rejections under 35 U.S.C. §112, Second Paragraph.**

The Examiner has rejected claims 1-8 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which application regards as the invention. The rejection is overcome in parts in view of the

amendments and traversed in pares. Claim 1 is amended to delete "numerical" and Claim 4 is amended to delete "small." As to "tag", the rejection is traversed. The expression "tag" refers to the fact that the primers can be degenerative (universal) primers, *i.e.*, primers which can bind to many different sites of a cell DNA. Examples of such primers are DOP or SiA primers (see specification at page 2, liens 9-11). Therefore, the §112, second paragraph rejection of Claims 1-8 should be withdrawn.

Claims 1-7 are rejected under 35 U.S.C. §112, second paragraph, as being incomplete for omitting essential steps. Claim 1 is amended to include the step of cohybridizing the DNAs from (a) and (c) to metaphase chromosome spreads from normal cells under suppression hybridization conditions. Therefore, the amended Claims 1-7 do not omit any essential step.

The Examiner also states that claim 8 is confusing with respect to just how the primers relate to the amplified DNA. Claim 8 is amended to recite that a kit comprising DNAs flanked by tag primers that are amplified from cells that have no known changes in their DNAs. Therefore, the §112, second paragraph rejection of Claim 8 should be withdrawn.

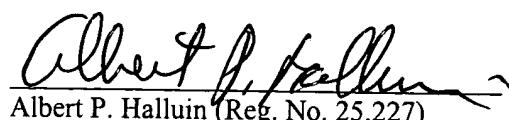
In view of the above amendments, Applicant respectfully requests the withdrawal of rejections under 35 U.S.C. §112, second paragraph.

#### CONCLUSION

It is now believed that the claims are in condition for allowance and advancement as such is earnestly requested. Should any questions arise in connection with this submission which may be resolved by a telephonic interview, the Examiner is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

Date: September 25, 2000



Albert P. Halluin (Reg. No. 25,227)

**HOWREY SIMON ARNOLD & WHITE, LLP**  
Box No. 34  
1299 Pennsylvania Avenue, N.W.  
Washington, D.C. 20004-2402  
(650) 463-8109